REMARKS

Reconsideration of this application is respectfully requested in view of the foregoing amendment and the following remarks. Claims 1-29 were pending in this Application. Claims 4 and 18-29 have been cancelled, claims 30-40 have been added, and claims 7 and 9-16 remain withdrawn. Claims 1-3 and 5-17 have been amended. Accordingly claims 1-3, 5-6, 8, 17 and 30-40 are presently under examination. For the reasons set forth below, Applicant respectfully submits that all claims pending herein are in condition for Allowance.

The Present Invention

Applicant respectfully submits that the present invention derives in part from the recognition that the cells of individuals having certain specific neurological conditions exhibit less effective G1/S cell cycle checkpoint control than do the cells of normal healthy individuals. This difference provides a novel means for discerning whether a subject is normal or has a neurological condition.

Amendments to the Claims

Claim 1 has accordingly been amended to recite a method for diagnosing specific neurological conditions discussed in the specification: Alzheimer's disease; incipient Alzheimer's disease; possible Alzheimer's disease; and Alzheimer's disease associated with evidence of other type of dementia. As the Examiner will note, the claim now recites that a non-neuronal cell of a subject is to be analyzed for the effectiveness of its G1/S cell cycle checkpoint, and that the determined effectiveness is to be compared with that of either: (A) a cell of a normal healthy individual (thereby permitting a diagnosis of whether the subject is normal) or (B) a cell of an individual having the specific neurological condition of interest (thereby permitting a diagnosis of whether the subject has that condition).

Dependent claims 2, 3, 5 and 8 have been amended to correct matters of antecedent basis relating to their ultimate dependency on amended claim 1, and to clarify the claim language. Claim 6 has been amended to correct the spelling of "ionizing", and claim 8 has been amended to

remove a phrase no longer applicable because claim 8 no longer depends from claim 5. Claims 17 and 18 have been amended to depend from both claims 1 and 2.

Non-elected claims 7 and 9-16 have been amended to correct matters of antecedent basis relating to their dependencies including their ultimate dependency on amended claim 1, and to clarify the claim language. New claims 33 and 35-40 are drawn to the non-elected inventions of Groups I and III-VII, as set forth in the Office Action of September 19, 2006, and are therefore also linked to the elected invention of Group II by linking claims 1-6 and 17. The amendment of these withdrawn claims, and the new claims to these non-elected groups are respectfully requested to be entered for the purposes of expediting prosecution upon rejoinder pursuant to MPEP § 821.04.

New claims 30-32 and 34 are drawn to the elected invention and examination thereof is respectfully requested.

Support for the amendments and new claims may be found, for example, in the original claims, and in the specification at page 3, line 10 to page 6, line 20; page 9, line 10 to page 10, line 21; and page 23, line 14 to page 30, line 12. No new matter has been introduced by any of the requested amendments.

Rejection under 35 USC § 112, First Paragraph (Enablement)

In the Office Action, claims 1-6, 8, 17 and 18 were rejected under 35 U.S.C. § 112, first paragraph as allegedly not being enabled by the specification. To the extent this rejection might still be applied to claims presently pending in this Application, it is respectfully traversed, and reconsideration is requested.

Two bases for the rejection have been advanced in the Office Action: that the art is unpredictable, as evinced by the inability to "definitely" diagnose Alzheimer's Disease prior to death and by allegedly contradictory data in the present Application and a publication by the inventor; and that the present Application fails to provide those of ordinary skill with sufficient

guidance to enable the diagnosis of Alzheimer's Disease (as opposed to cancer) by determining the effectiveness of the G1/S cell cycle checkpoint in non-neuronal cells.

As discussed in the accompanying Declaration of Dr. Zsuzsanna Nagy, the present Application indeed provides a method of diagnosing that is as reliable as other diagnostic methods in the art, there is no contradictory data, and there is sufficient guidance both in the Application and in the general knowledge of those skilled in the art to enable the diagnosis of the recited neurological diseases using the claimed methods.

As Dr. Nagy advises, the claimed methods are useful for diagnosing the recited neurological diseases with at least as much specificity as other pre-death methods currently used in the art, such as the NINCDS-ARDRA criteria, which have a 98-100% positive predictive value when followed by post-mortem examination. Thus, Dr. Nagy advises that a diagnostic practitioner skilled in the art would consider the claimed methods at least as reliable as the NINCDS-ARDRA criteria for identifying subjects with Alzheimer's disease prior to death. Applicant also respectfully submits that a patented invention need not be the *best* way of accomplishing a goal. *See Carl Zeiss Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 U.S.P.Q.2d 1094, 1100 (Fed. Cir. 1991) ("An invention need not be the best or the only way to accomplish a certain result..."). Indeed, in the field of Alzheimer's disease, the best diagnostic is a post-mortem examination of the brain, but when therapeutic intervention is desired prior to death, diagnosticians often rely on less than perfect means. Declaration of Zsuzsanna Nagy, Ph.D., Pursuant to 37 C.F.R. § 1.132 ("Nagy Declaration"), at paragraphs 7-10.

Dr. Nagy also advises that the data in the Application does not contradict the data found in the publication entitled "Cell Cycle Kinesis in Lymphocytes in the Diagnosis of Alzheimer's Disease", Neuroscience Letters 317:81-84 (2002) (the "2002 Publication"). She explains that while there is normal experimental variance in the data, the results of both sets of experiments are consistent, and permit a reliable use of relative G1 lengthening as a diagnostic for Alzheimer's Disease. Nagy Declaration, at paragraphs 12-16.

Further, Dr. Nagy addresses the Office Action's argument regarding potential misdiagnosis of cancer patients, by explaining how the claimed methods would not lead to misdiagnosing cancer patients. She explains that the claimed methods are able to use non-neuronal, non-diseased cells to diagnose Alzheimer's disease, but that because cancer cells do not produce the cell cycle effects used in the claim methods *in non-cancerous cells*, use of the claimed methods would not lead to misdiagnoses. Nagy Declaration, at paragraphs 18-19.

Dr. Nagy also addresses the Office Action's concern regarding the ability of ionizing and UV radiation to arrest cells in the G1 phase, by citing references in the art supporting her opinion that these types of radiation do indeed arrest cells in G1. Nagy Declaration, at paragraph 21. Copies of the references she cites are attached to the Nagy Declaration.

A reasonable analysis of the *In re Wands* criteria also supports Applicant's position that no undue experimentation would be required to make and use the claimed invention. *See In re Wands*, 858 F.2d 731, 737, 8 U.S.P.Q.2d 1400, 1404 (Fed. Cir. 1998). The first *Wands* criterion is the quantity of experimentation necessary. The "make-and-test" quantum of experimentation is reduced by the extensive knowledge, *e.g.*, of cell cycle regulation, cell culture systems, immunohistochemistry, FACS and other molecular biology laboratory techniques, to which a person of ordinary skill in the art has access. Performing routine and well-known steps, such as FACS analysis to confirm G1 lengthening cannot create undue experimentation even if it is laborious. *See In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 218-219 (C.C.P.A. 1976).

The second and third *Wands* criteria relate to the amount of direction or guidance given, and the presence or absence of working examples. The Office Action states that because of "no direction or guidance" as well as "no working examples", it would require undue experimentation by one skilled in the art to make and use the invention. Office Action at 5. The Office Action also states that "[the] disclosed working examples require a prior diagnosis of patients using the NINCDS criteria." *Id.* Applicant respectfully disagrees and directs the Office's attention to the present specification, where guidance is in fact provided in the form of working examples describing the use of the claimed methods to diagnose Alzheimer's disease

and the other recited neurological diseases, which diagnosis *was confirmed by* the independent diagnosis of the patients using the NINCDS-ARDRA criteria. *See, e.g.*, Example 1 at page 23, line 14 to page 30, line 12, particularly page 29, line 25 to page 30, line 12, and more particularly the passage at page 25, lines 18-19: "All experiments were carried out blind to the clinical diagnosis of the patients. The results were analyzed *in relation to the clinical diagnosis*..." (emphasis added). Example 1 can therefore be seen to be an independent diagnostic method, the validity of which was confirmed by comparison to a known clinical diagnostic method. This *confirmation* does not undermine the validity of the experimental (and claimed) diagnostic method itself.

The fourth through seventh *Wands* criteria focuses on the nature of the invention, the state of the art, the relative skill in the art, and the predictability of the art. The Office Action alleges that the level of skill in diagnosis is low, and that the art is unpredictable. Office Action at 6. Applicant respectfully disagrees and asserts, as discussed *supra* and in the Nagy Declaration, that the specification discloses sufficient guidance to render the results predictable. The present invention relates to molecular biology, cell cycle regulation, and methods related thereto. The nature of the invention is diagnostic molecular biology, which is a well-advanced field, and is not made unpredictable merely because a 100% "definitive" diagnosis of Alzheimer's disease cannot be made until post-mortem examination. Moreover, practitioners in this art are guided by considerable knowledge and resources on the conditions and approaches that can be utilized to examine regulation of the cell cycle, such as the immunohistochemistry and FACS methods described in the specification, *e.g.*, at page 9, line 10 to page 10, line 21 and page 23, lines 1-36.

The eighth criterion focuses on the breadth of the claims. Enablement is satisfied when the disclosure "adequately guide[s] the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility." *In re Vaeck,* 947 F.2d 488, 496, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991). In the present case, one of skill in the art is specifically guided by the disclosure to look to, *e.g.*, dysregulation of the

cell cycle at the G1/S cell cycle checkpoint to diagnosis, for example, Alzheimer's Disease, and particularly to the relative lengthening of the G1 phase in non-neuronal cells, which guidance parallels the scope of the claimed methods.

With respect to the Office's concern regarding the scope of the claims with respect to alleged coverage of increased and decreased effectiveness of the G1/S cell cycle checkpoint, Applicant respectfully disagrees with the Office's characterization of the cell cycle checkpoint. The G1/S cell cycle checkpoint is a checkpoint, *i.e.*, it halts the cell cycle. Any purported increase in its effectiveness would not be measurable, in that the cell cycle is still halted. Only decreases in checkpoint effectiveness are measurable using the claimed methods. Thus, while there can be decreased effectiveness of the checkpoint, there can be no increase in effectiveness, and accordingly the original claims accurately described the relationship between the claimed methods of measuring a G1/S cell cycle checkpoint defect (which is necessarily a decreased effectiveness) and diagnosing Alzheimer's disease. In the interest of furthering prosecution, however, Applicant has amended the claim language to recite a decreased effectiveness of the cell cycle checkpoint, and maintain that these amended claims, while of the same scope as the original claims, address the Office's concern.

Accordingly, for at least these reasons, the enablement rejection under 35 USC § 112, first paragraph, is traversed, and withdrawal of this rejection is respectfully requested.

Rejection under 35 USC § 112, Second Paragraph (Indefiniteness)

Claim 8 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In particular, claim 8 has been rejected due to the recitation of the phrase "stimulus that induces cell cycle arrest", for an alleged lack of antecedent basis.

Claim 8 has been amended to delete this phrase "stimulus that induces cell cycle arrest", which was in the claim due to a prior dependency that has since been changed. As amended, it is

submitted that claim 8 complies with 35 U.S.C. § 112, second paragraph, and withdrawal of this rejection is respectfully requested.

In view of the foregoing, all of the claims in this case are believed to be in condition for allowance. Should the Examiner have any questions or determine that any further action is desirable to place this application in even better condition for issue, the Examiner is encouraged to telephone Applicant's undersigned representative.

Dated: August 6, 2007

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